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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/865,993	05/25/2001	Brett P. Monia	RTS-0175	5849

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/865,993	MONIA ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *8-7-03*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-10, 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office action is in response to the communication filed 8-7-03.

Claims 1, 2, 4-10, 12-15 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1, 12, 13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for the reasons of record set forth in the Office action mailed 5-7-03.

Applicant's arguments filed 8-7-03 have been fully considered but they are not persuasive. Applicants argue that the term *compound* is well recognized by those skilled in the art and can be found in numerous dictionaries. Contrary to Applicants' assertions, and with respect to the instantly claimed invention, the term compound is defined very broadly in numerous dictionaries and determining the metes and bounds of the claimed invention is not aided by a lay definition provided in numerous dictionaries, as suggested by Applicant. The instant disclosure describes antisense oligonucleotides that specifically target and inhibit the expression of the target gene DUSP5 in vitro. The broader genus, *compound*, however, presumably includes within it antisense oligoncucleotides, as well as other chemical entities that are not adequately described or delineated in the instant application, and hence whose metes and bounds cannot be

determined from the language of the claims, from the instant disclosure, or from numerous dictionaries. Therefore, the instant rejection is maintained.

Claims 1, 2, 4-10, 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishibashi et al and Sato et al, in view of Milner et al and Baracchini et al for the reasons of record set forth in the Office action mailed 5-7-03.

Applicant's arguments filed 8-7-03 have been fully considered but they are not persuasive. Applicants argue that the obviousness rejection of record is improper because, Applicants assert, the requisite motivation (or motivating force) must stem from some teaching, suggestion or inference in the prior art as a whole and furthermore that no reasons were provided as to why one of ordinary skill would have been led to combine the cited teachings of Ishibashi, Sato, Baracchini and Milner to arrive at the claimed invention. Contrary to Applicants' assertions, the teaching of Ishibashi et al provides ample motivation to inhibit the expression of DSP5 because of this molecule's possible role in cellular signal transduction and cell cycle regulation, and ultimately in cell growth control. Ishibashi et al teach the enhanced expression of DSP5 in stressed cells, implicating DSP5 in cellular survival responses to stress, which response, "if left unchecked, would lead to severe damage and eventually to cell death." (right hand col. on page 29,901). Sato et al teach the increased expression of DSP5 in cells in the presence of increased concentrations of lysophosphatidylcholine, which is a proatherogenic agent, and which is present in atherosclerotic lesions. Sato therefore provides further motivation to inhibit the expression of DSP5 in appropriate target cells

by identifying DSP5 as a potential mediator in atherogenesis, Taken together, the teachings of Ishibashi and Sato provide the requisite motivation to inhibit the expression of DSP5.

Applicants argue that the prior Office action's reasoning leads to the conclusion that once a protein target is known, then all compounds having 8-50 nucleobases targeting the nucleic acid encoding the protein would be obviously used to inhibit the protein's expression. Applicants' arguments are persuasive in part. Once the nucleotide sequence encoding a protein has been disclosed, and once the motivation to inhibit that particular protein has been provided (as in the instant case linking the increased expression of DUS5 with cell survival under stress, or the correlation of increased expression of DUS5 in a particular pathological state, as here in atherogenesis), then the ability to design and assess antisense for their ability to inhibit the expression of this target gene requires only routine experimentation, rendering the claimed invention obvious to one of ordinary skill in the art. As discussed above, the motivation to inhibit the expression of DSP5 has been provided by the teachings of Ishibashi and Sato. Milner teaches the design and assessment of antisense, including those between 8-50 nucleobases in length, to target a known nucleotide sequence and inhibit its expression in vitro. This method of in vitro antisense inhibition of a previously characterized nucleic acid of known nucleotide sequence taught by Milner is now routine in the art, and hence it would only require routine experimentation to determine which antisense are able to inhibit the target gene's expression by 40% or greater. One of ordinary skill in the art would have a reasonable expectation of success in finding a

subset of antisense that successfully inhibit the expression of the target gene of known nucleotide sequence, such as DSP5, in vitro, using routine and well established methods. Such routine experimentation renders the instant invention obvious, and not, as Applicants assert, obvious to try.

Applicants assert that focusing on the obviousness of substitutions and differences in various references, rather than focusing on the invention as a whole, is a legally improper way to simplify the difficult determination of obviousness, because, according to Applicants, the Office action relies only on hindsight reconstruction of the instant specification to provide the motivation to render the claimed invention obvious. Contrary to Applicants' assertion, the teachings in the art (i.e. Ishibashi and Sato) provide sufficient motivation to inhibit the expression of DSP5, because these references teach a correlation in increased expression of DSP5 under conditions of cellular stress and in a pathological state. Furthermore, Ishibashi provides the nucleotide sequence of DSP5. This teaching, together with the routine experimentation taught previously by Milner, render the method of inhibiting the expression of DSP5 in vitro using antisense between 8-50 nucleobases obvious. As for the allegation that only portions of one reference have been substituted for another in order to devise an obviousness rejection, Milner teaches a general technique for designing and assessing the ability of various antisense to target and inhibit the expression of a known target gene, and this technique is not limited in any way to a particular antisense molecule or a particular target gene, but rather is a technique that is applied routinely to any target gene of known nucleotide sequence. Regarding the "particular element" extracted from

the Ishibashi reference that is alleged by Applicants, the entire thrust of this reference is directed to the cloning, isolation and characterization of DSP5, and its induction under conditions of cellular stress. It is therefore unclear why Applicants assert that any "particular element" has been extracted and used for constructing an obviousness rejection based on hindsight reasoning. The nucleotide sequence, the increased expression under conditions of cellular stress, and the motivation to study and inhibit the expression of the featured DSP5 molecule are disclosed in the Ishibashi reference. This is not an example of picking one particular element from a reference for constructing hindsight reasoning, as asserted by Applicants.

In addition, the Baracchini reference has been cited – not because one particular element has been taken out of context in order to construct an obviousness rejection out of hindsight using the instant specification as a blueprint, as suggested by Applicants – but rather to teach the general applicability of various modifications incorporated into antisense to enhance their stability, target binding and cellular uptake. The modifications disclosed by Baracchini et al (e.g. phosphorothioate internucleotide linkages, nucleobase and sugar modifications, chimeric antisense, colloidal dispersions of antisense oligonucleotides) are not limited to an antisense of a particular sequence, but can be incorporated into antisense targeting any gene sequence, and these modifications have been generally applied to the field of antisense, independent of oligonucleotide sequence. Therefore, the references of Ishibashi, Sato, Baracchini and Milner together provide the general knowledge and motivation that render the claimed invention obvious to one of ordinary skill in the art.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is 703-872-9306. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(517) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SEAN McGARRY
PRIMARY EXAMINER

JZ
1-21-04